

Clinical Aspects of Comorbid Schizophrenia and Idiopathic Parkinson's Disease

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Abstract

The comorbidity of schizophrenia and idiopathic Parkinson's disease (IPD) is illustrated by a case description of a schizophrenic patient who develops motor symptoms finally diagnosed and treated as comorbid IPD. Several aspects of the clinical challenges of this comorbidity are discussed and an overview of earlier reported cases is presented. IPD must be distinguished from neuroleptic-induced parkinsonism by clinical course and characteristics. A SPECT scan is helpful for diagnosis. We recommend antiparkinsonian treatment to be prescribed only with the protection of antipsychotic agents, of which clozapine and quetiapine are the best choices.

Key Words: Antipsychotic Agents, Comorbidity, Levodopa, Parkinson's Disease, Schizophrenia

Introduction

According to the dopamine hypothesis of schizophrenia, its positive symptoms (such as delusions and hallucinations) arise from increased dopamine activity (1, 2). In contrast, hypodopaminergic transmission is the underlying mechanism of idiopathic Parkinson's disease (IPD). Several patients with both schizophrenia and IPD have been described (3-12). The apparent paradox of the co-existence of schizophrenia (hyperdopaminergic) and IPD (hypodopaminergic) can probably be explained by dopaminergic neurons projecting to the motor striatum, and those projecting to association regions being affected independently (10): in IPD, degeneration occurs primarily in midbrain dopaminer-

gic neurons, whereas dopaminergic neurons in other brain regions are less vulnerable to degeneration (13). It is less clear why so few patients with both conditions have been described. Millions of individuals exist with either schizophrenia or IPD and yet there are only a handful of reported cases of the co-existence.

Apart from these theoretical aspects, in clinical practice the combination of schizophrenia and IPD in one individual presents a challenge to clinicians. First, when confronted with a schizophrenic patient displaying a movement disorder resembling IPD, clinicians have to differentiate between neuroleptic-induced parkinsonism (NIP) and IPD. Second, when schizophrenia and IPD are eventually co-diagnosed, clinicians have to find a balance in the pharmacotherapy of the two disorders: antipsychotics block dopaminergic neurotransmission, thereby increasing the symptoms of IPD, whereas antiparkinsonian drugs can exacerbate psychosis by enhancing dopaminergic neurotransmission. In this article we present a case report of comorbid schizophrenia and IPD. The clinical implications are discussed and a concise review of other reported cases also in comparison to our case is presented.

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Submitted: April 15, 2011; Revised: October 7, 2011;

Accepted: October 26, 2011

Case

A male, now 55 years old, had his first psychotic episode in his thirties. During that episode, while under the influence of imperative auditory hallucinations, he stabbed an innocent bystander. He was diagnosed with paranoid schizophrenia and was sentenced to forced treatment in a forensic setting. Fluphenazine depot 25 mg every four weeks was started and continued since. After three years, he was discharged home and received outpatient treatment. Delusions and hallucinations disappeared and did not recur for more than 25 years. However, several symptoms remained, such as disorganization of speech, inadequate affect, social withdrawal and impaired personal self-care. He remained unemployed and has always lived alone.

In 2005 (at age 49), the first remark on a tremor was noted in his patient record. No details about the tremor are mentioned initially. His symptoms did not improve with a variety of pharmacological interventions such as successive addition to the depot of several anticholinergic agents, a COMT-blocker and a dopamine reuptake inhibitor. The dose of fluphenazine was slightly reduced to 22.5 mg every four weeks. Unfortunately, no further examination or treatment is mentioned in the patient record for about two years.

In 2007, the tremor appeared to have progressed and was located in the arms, hands, legs and chin. The tremor was asymmetric with the right side being more affected than the left. There was a resting pill-rolling tremor, as well as a postural tremor. Slight rigidity was present in both legs. There was no hypokinesia or bradykinesia. No improvement was obtained by prescription of a β -blocker or by a second slight reduction of the depot to 18.5 mg every four weeks. On neurological referral, NIP, an incipient IPD (in view of the asymmetry of the tremor and the resting tremor that included the thumbs) and a possibly co-occurring essential tremor (in view of the prominent involvement of the chin and the postural tremor) were considered as possible diagnoses. There was no family history of movement disorders. An MRI of the brain was normal. Levodopa/carbidopa (150/37.5 mg daily) was prescribed, but it was not clear if the patient took the medication for more than a few weeks.

In 2008, the tremor was clearly visible and incapacitating. The same differential diagnosis was made as stated above, but for several reasons the possibility of IPD was considered as most likely: 1) the symptoms started first after more than 20 years of relatively low-dosed antipsychotic treatment; and, 2) the symptoms were progressive and did not diminish after lowering neuroleptic treatment. Treatment options were presented to the patient and his family several times. They were opposed to any changes and expressed concern that a recurrence of psychosis would lead to further violence. They argued being told the medication

should never be stopped. They were also opposed to switching to clozapine because of its possible side effects. In addition, the patient himself mostly feared having to be admitted in case of side effects given his earlier negative experiences. Also, in spite of the tremor being incapacitating, he was ambivalent about treatment of the tremor. Finally, they agreed to gradually taper fluphenazine to zero over a period of six months without replacement by another antipsychotic agent.

The last dose of depot was administered in July 2008. In theory, the washout of a drug takes 5 times the half-life (in the case of fluphenazine, $5 \times 7-14$ days is 35–70 days) (14). However, in some schizophrenic patients participating in a depot withdrawal study, fluphenazine was still detectable about six months after discontinuation of the depot (15). Discontinuation of fluphenazine did not lead to any improvement of the patient's tremor over a period of seven months. He developed minor complaints of hyperesthesia and appeared to withdraw himself further from social contacts. No positive psychotic symptoms recurred though. In November 2008, a SPECT scan showed evidence of the presence of IPD, which made it even less likely that the depot antipsychotic was the cause of the movement disorder.

In February 2009, again after extensive deliberations with the patient and his family during which they still objected to clozapine, a combination preparation of levodopa/carbidopa was prescribed and gradually built up to a dose of 300/75 mg daily by July 2009. We decided the patient could be safely treated with dopaminergic medication without antipsychotic protection (after cessation of the depot) because of close involvement of the family and the possibility of strict follow-up. Three months later, no change was noticed in either his psychiatric or his neurological state. In November 2009, the COMT-blocker entacapone (600 mg daily) was added in a combination with levodopa/carbidopa (now at 450/112.5 mg daily). Finally, in June 2010, the tremor practically disappeared with virtually no rigidity remaining. However, at the same time the patient displayed worsening of speech disorganization, agitation, irritability, hyperesthesia and paranoid thinking. Levodopa/carbidopa/entacapone was reduced to 300/75/200 mg daily. The patient finally consented to hospital admission for clozapine treatment. Probably due to the reduction of antiparkinsonian medication, the tremor immediately reappeared. Clozapine treatment was complicated by pneumonia and toxic clozapine plasma concentrations requiring admission to a general hospital and temporary cessation of clozapine. No agranulocytosis occurred during this episode. Next, clozapine was reintroduced (up to 150 mg daily, plasma concentration: 150 ng/L). Simultaneously, levodopa/carbidopa/entacapone was gradually restored to 450/112.5/200 mg daily. On this regi-

men, the disordered speech returned to the same degree as in the period when the patient used the depot. At present, there are no delusions or hallucinations and the tremor is barely visible in daily life.

So it can be hypothesized (with the obvious limitation that this clinical course was observed in only a single patient) that when one induces synaptical dopamine levels required for adequate anti-parkinsonian therapeutic effect, these levels are sufficient to induce psychotic symptoms in a patient with schizophrenia.

Discussion

This case report illustrates the challenge to clinicians of the comorbidity of schizophrenia and IPD. Several critical comments can be made on the clinical management of this case. First, the path toward the final diagnosis could have been shorter. In general, when parkinsonian symptoms develop in a patient chronically treated with antipsychotics for schizophrenia, one should consider not only NIP (most probable in the vast majority of the cases) but also IPD as possible diagnosis. It is often stated that if the symptoms do not disappear after adequate intervention (e.g., anticholinergics or antipsychotic dose reduction), the symptoms start and remain asymmetric and respond well to dopamine treatment, then the clinical course and symptoms are more suggestive of IPD than of NIP. However, it is not clear whether IPD and NIP can be distinguished merely by clinical features. Hassin-Baer et al. state that IPD symptoms tend to be asymmetric, whereas NIP in general is symmetrical; a rest tremor is present more frequently in IPD than in NIP; and, IPD can affect the entire body, whereas NIP usually affects only the upper half of the body (16). This suggests that IPD could be distinguished from NIP in the majority of the cases. On the contrary, Lorberboym et al. report no differences in clinical features between 9 patients with and 11 without SPECT proven degeneration of the nigrostriatal system, thus indicating that drug-induced parkinsonism (DIP) is clinically indistinguishable from IPD (17). We can conclude that there is an overlap between DIP and IPD in the clinical picture and that—in case of doubt—a SPECT scan should be performed. In this case, a SPECT scan could have been arranged earlier.

Second, the pharmacological treatment in the time period preceding the definite diagnosis of IPD including

SPECT scan (before 2008) could be criticized. The prescription of a variety of antiparkinsonian drugs promoting dopaminergic transmission (including a dopamine reuptake inhibitor) together with antipsychotics (blocking dopaminergic transmission) in that period was not rational. Third, one might wonder if we could have been more effective in educating and persuading the patient and his family. As remarked, the patient himself was ambivalent on the burden of his IPD and was strongly opposed to any change in his (classical antipsychotic!) medication and to the commencement of any treatment that might lead to admission in a clinic (clozapine). Also, the strategy to treat the patient with parkinsonian medication only can be debated, and is probably not applicable in many patients. Although one might argue this patient remained stable for a surprisingly long time on a relatively large dosage of dopaminergic drugs alone, this strategy proved unproductive over the long term: IPD symptoms eventually disappeared, but psychotic symptoms occurred, necessitating antipsychotic treatment. We were struck by the observation that at the very point the antiparkinsonian drugs started to have a therapeutic effect, the patient also began to experience psychotic symptoms. So it can be hypothesized (with the obvious limitation that this clinical course was observed in only a single patient) that when one induces synaptical dopamine levels required for adequate antiparkinsonian therapeutic effect, these levels are sufficient to induce psychotic symptoms in a patient with schi

After diagnosis of IPD in a schizophrenic patient the next issue is which antipsychotic to choose. Only a few reported cases on patients with comorbid schizophrenia and IPD are available, but no larger studies. In choosing an antipsychotic, the literature about psychosis in IPD, whether drug induced or not, might provide some insight. If antipsychotic treatment for psychotic phenomena in IPD is necessary, then quetiapine is recommended as the first choice; clozapine and olanzapine are second and third choices, respectively, whereas risperidone should be avoided because it is poorly tolerated (18). In line with this, in a U.S. study 66% of IPD patient treated with antipsychotics received quetiapine, but clozapine was rarely prescribed (2%) (19). However, no beneficial effect of quetiapine was shown in a double-blind, placebo-controlled trial in IPD patients (20). Furthermore, worsening of motor symptoms due to quetiapine is reported in one case of comorbid schizophrenia and IPD (11). In contrast to the predominant use of quetiapine in the U.S., the Dutch IPD guideline recommends clozapine as the first-choice antipsychotic (21). Based on this guideline, we decided to prescribe clozapine to our patient.

Comparison of our case to other reported cases of the comorbidity of schizophrenia and IPD is possible since

Table 1 Characteristics of 8 Earlier Reported Cases of Comorbidity of Schizophrenia and IPD

Case Report (ref #)	Diagnosis of IPD (sex, age of onset)	Psychosis during IPD Medication	Reaction of IPD to			Clinical Outcome (authors' recommendations)
			FGA	SGA	CLZ	
Friedman (3, 4)	Clinical, autopsy confirmed (♂, 32)	Yes	↑↑	×	=	Mild IPD symptoms and controllable residual psychotic symptoms with levodopa/carbidopa & clozapine.
Lam (5)	Clinical diagnosis: NIP; autopsy: IPD (♀, 58)	Yes	↑↑	×	=	Some improvement of IPD; psychotic symptoms responsive to loxapine.
Höfllich (6)	Clinical, SPECT (♀, 43)	Yes	↑	↑	=	Improvement of psychosis & IPD after 10 sessions of ECT. (Think of ECT for treatment in these cases.)
Schwarz (7) patient 1	Clinical, SPECT (♀, 38)	Yes	×	×	=	No change in motor function; outcome of psychosis not reported. (Perform SPECT for diagnosis of IPD.)
Schwarz (7) patient 2	Clinical, SPECT (♂, 58)	No	↑	×	=	Improvement of IPD; psychosis adequately controlled with clozapine. (Perform SPECT for diagnosis of IPD.)
Orr (8)	Clinical (♂, 33)	×	↑↑	×	↓↓	Improvement of both IPD and psychosis with clozapine monotherapy.
Urban (9)	Clinical, SPECT, levodopa test (♀, 47)	×	↑	↑	=	×
Winter (10)	Clinical, SPECT (♂, 35)	×	×	×	×	×
Habermeyer (11)	Clinical, SPECT (♂, 64)	Yes	×	↑	×	Good motor control & stable mental state with levodopa, entacapon & quetiapine. (Perform SPECT for diagnosis of IPD.)
Fujino (12)	Clinical (♀, 71)	Yes	×	↓	×	Improvement of both IPD and psychosis with aripiprazole monotherapy.

CLZ: clozapine; ECT: electroconvulsive treatment; FGA: first-generation antipsychotic; IPD: idiopathic Parkinson's disease; NIP: neuroleptic-induced parkinsonism; SGA: second-generation antipsychotic; SPECT: single photon emission computed tomography.

↑: worse; ↑↑: much worse; =: no change; ↓: better; ↓↓: much better; ×: not reported /not applicable

details about symptoms, clinical course and medication strategies are available in the listed papers. In Table 1 we present a concise overview of the other reported cases. Including our patient, data on 11 patients (6 females, 5 males) are available. Mean age of onset of psychotic symptoms is 26.8 (range: 19–40) and age of onset of IPD symptoms is 47.4 years (range: 32–64). Resting tremor and rigidity are the most frequent initial symptoms. Asymmetric symptoms are present in at least 5 patients. Ten out of 11 patients were diagnosed first with schizophrenia and afterward the diagnosis of IPD was made. In the oldest published cases, the diagnosis is based on clinical evaluation (3, 5). In two cases, the IPD diagnosis was eventually confirmed by autopsy (4, 5), with one of those having had clinical diagnosis of DIP

during life. Diagnostic confirmation of a SPECT scan is presented in most cases published since 1994 (6, 7, 9–11). It is important to note that almost all reported cases show remaining or recurrent psychotic symptoms after diagnosis of IPD. Treatment with antiparkinsonian drugs without protection of antipsychotics for a considerable period of time as reported in our case is a unique point compared to the other cases. The failure of this strategy, however, emphasizes the necessity of antipsychotic protection. Furthermore, it is not surprising that worsening of motor symptoms due to first- and second-generation antipsychotics is described in all applicable cases, whereas no negative influence of clozapine on motor symptoms is described. In general, clinical outcome in most reported cases is similar to our case: a

pharmacological balance appeared to be found between antipsychotic and antiparkinsonian drug effects with reasonably good outcome with respect to both schizophrenia and IPD. Two interesting cases showed improvement of both psychotic and parkinsonian symptoms with either clozapine or aripiprazole monotherapy (8, 12). If pharmacological strategies fail, electroconvulsive therapy (ECT) might be an option. ECT turned out beneficial for both psychotic and IPD symptoms in one case (6).

Conclusions

Comorbidity of schizophrenia and IPD in one patient requires careful examination, treatment and follow-up. IPD must be distinguished from NIP by clinical course and characteristics. A SPECT scan is helpful in inconclusive cases. Based both on this and earlier reported cases, we can conclude that antiparkinsonian treatment should be prescribed only with the protection of antipsychotic agents, of which clozapine and quetiapine are the best choices.

References

1. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophr Bull* 2009;35(3):549-562.
2. Kegeles LS, Abi-Dargham A, Frankle WG, Gil R, Cooper TB, Slifstein M, et al. Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. *Arch Gen Psychiatry* 2010;67(3):231-239.
3. Friedman JH, Max J, Swift R. Idiopathic Parkinson's disease in a chronic schizophrenic patient: long-term treatment with clozapine and L-dopa. *Clin Neuropharmacol* 1987;10(5):470-475.
4. Friedman JH, Fernandez HH. Autopsy follow-up of a patient with schizophrenia and presumed idiopathic Parkinson's disease. *Clin Neuropharmacol* 2001;24(2):120-121.
5. Lam RW. Chronic schizophrenia and idiopathic Parkinson's disease. *Can J Psychiatry* 1993;38(2):75-77.
6. Hoflich G, Burghof KW, Kasper S, Moller HJ. [Electroconvulsive therapy in comorbidity of treatment refractory paranoid hallucinatory psychoses with Parkinson disease]. *Nervenarzt* 1994;65(3):202-205. German.
7. Schwarz J, Scherer J, Trenkwalder C, Mozley PD, Tatsch K. Reduced striatal dopaminergic innervation shown by IPT and SPECT in patients under neuroleptic treatment: need for levodopa therapy? *Psychiatry Res* 1998;83(1):23-28.
8. Orr G, Munitz H, Hermesh H. Low-dose clozapine for the treatment of Parkinson's disease in a patient with schizophrenia. *Clin Neuropharmacol* 2001;24(2):117-119.
9. Urban A, Libiger J, Hosak L, Kupka K. Comorbidity of parkinsonism and schizophrenia in a patient treated with clozapine. *Eur Psychiatry* 2003;18(5):258-259.
10. Winter C, Juckel G, Plotkin M, Niehaus L, Kupsch A. Letter to the editor: Paranoid schizophrenia and idiopathic Parkinson's disease do coexist: a challenge for clinicians. *Psychiatry Clin Neurosci* 2006;60(5):639.
11. Habermeyer B, Kneifel S, Lotz-Blauer I, Muller-Spahn F. Psychosis in a case of schizophrenia and Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 2008;20(3):373-375.
12. Fujino J, Tanaka H, Taniguchi N, Tabushi K. Effectiveness of aripiprazole in a patient with presumed idiopathic Parkinson's disease and chronic paranoid schizophrenia. *Psychiatry Clin Neurosci* 2010;64(1):108-109.
13. Liang CL, Wang TT, Luby-Phelps K, German DC. Mitochondria mass is low in mouse substantia nigra dopamine neurons: implications for Parkinson's disease. *Exp Neurol* 2007;203(2):370-380.
14. Taylor D. Psychopharmacology and adverse effects of antipsychotic long-acting injections: a review. *Br J Psychiatry Suppl* 2009;52:S13-19.
15. Wistedt B, Jorgensen A, Wiles D. A depot neuroleptic withdrawal study. Plasma concentration of fluphenazine and flupenthixol and relapse frequency. *Psychopharmacology (Berl)* 1982;78(4):301-304.
16. Hassin-Baer S, Sirota P, Korczyn AD, Treves TA, Epstein B, Shabtai H, et al. Clinical characteristics of neuroleptic-induced parkinsonism. *J Neural Transm* 2001;108(11):1299-1308.
17. Lorberboym M, Treves TA, Melamed E, Lampl Y, Hellmann M, Djaldetti R. [123I]-FP/CIT SPECT imaging for distinguishing drug-induced parkinsonism from Parkinson's disease. *Mov Disord* 2006;21(4):510-514.
18. Friedman JH, Factor SA. Atypical antipsychotics in the treatment of drug-induced psychosis in Parkinson's disease. *Mov Disord* 2000;15(2):201-211.
19. Weintraub D, Chen P, Ignacio RV, Mamikonyan E, Kales HC. Patterns and trends in antipsychotic prescribing for Parkinson disease psychosis. *Arch Neurol* 2011;68(7):899-904.
20. Rabey JM, Prokhorov T, Miniovitz A, Dobronevsky E, Klein C. Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration. *Mov Disord* 2007;22(3):313-318.
21. Bloem BR, Van Laar T, Keus SHJ, de Beer H, Poot E, Buskens E, et al. [Multidisciplinary guideline Parkinson's disease]. Dutch. 2010; available at: http://www.cbo.nl/Downloads/880/rl_parkinson_10.pdf.